Author's response to reviews

Title: Ipsilateral Lower Extremity Joint Involvement Increases the Risk of Poor Pain and Function Outcomes after Hip or Knee Arthroplasty

Authors:

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Author's response to reviews: see over
We thank the reviewers for their valuable and insightful comments. These have really helped us improve the quality of our paper. Following are our point-by-point responses to the comments.

Reviewer’s report

Title: Ipsilateral Lower Extremity Joint Involvement Increases the Risk of Poor Pain and Function Outcomes after Hip or Knee Arthroplasty

Date: 30 January 2013

Reviewer: David Beverland

Reviewer’s report:

TITLE
Ipsilateral Lower Extremity Joint Involvement Increases the Risk of Poor Pain and Function Outcomes after Hip or Knee Arthroplasty

1. Abstract Methods
Authors say “In this prospectively cohort study” should read “In this prospective cohort study”. Having read the paper I would have thought that this would be more accurately described as a retrospective study of prospectively collected data.

Response: We agree and have corrected this as suggested.

“Methods: In this retrospective study of prospectively collected data, we used the data from the Mayo Clinic Total Joint Registry to assess the association of ipsilateral knee or hip joint involvement with.....”

2. Introduction
Live 4, reference 2. I haven’t read the reference but the authors say “Primary THA and TKA exceeded 1.3 million in 2009”. The reference appears to have been published in 2007 so was this a mistake? Otherwise the Introduction is clear and well written.

Response: We agree and have corrected the error.

“The public health significance of joint arthroplasty is enormous, given that combined annual volume of primary THA and TKA exceeded 1.1 million in 2009 in the U.S. [1].”

3. Methods
Again note earlier comment on whether or not there was a retrospective nature to this study.

Response: We have made the change as suggested above in the abstract.

4. The patients were contacted in one of three ways 1 Questionnaires mailed to the patients 2 Administered during the clinic visit or 3 By telephone contact. I think it would be interesting for readers to know what proportion of patients at the Mayo clinic were contacted using each method. Presumably this has a major impact on the response rate assuming that there is 100% response rate from those patients who attend the clinic.

Response: The methods of survey (clinic, mail, telephone call) are usually applied in a logical sequence, and therefore the response rates are not directly comparable to each other. The time windows for mailing questionnaire prior to the clinic visit have changed slightly over the last 2 decades. The proportion of patients in the primary TKA and THA replacement with each mode of administration were as follows:
5. Predictor Variable and its Definition
-The authors say “The main predictor of interest was the presence of ipsilateral knee involvement”. I don’t think the authors actually define what they mean by involvement, for example, do the authors just take the patient’s word for it that their other joint is “involved” or is it confirmed that they have some pathology in that joint such as a degenerative change or a previous arthroplasty.
-Response: Ipsilateral knee involvement is defined based on patient response to the question “Please indicate if you activities are limited by other joints (mark all that apply): none, right hip, left hip, right knee and left knee.” We have clarified this construct by modifying the methods and results sections, as shown below.
-Patient reported outcomes are the current (gold) standard of assessment of outcome/success of knee and hip replacement surgeries. We are following the paradigm of patient-centered and patient-reported outcomes in this study, as is done in >90% of studies of THA and TKA outcomes of pain and function. Improvement in patient’s perception of pain and activity limitation is also probably one of the key reasons for the huge success of TKA and THA. There is no doubt that the underlying pathology leads to pain and function limitation in patients. However, the main reason for undergoing arthroplasty (an elective procedure) is patient experience of improvement in pain and activity limitation (self-reported function) after TKA and THA.

“The main predictor of interest was the presence of ipsilateral knee involvement associated with activity limitation for patients with THA and ipsilateral hip involvement associated with activity limitation for patients with TKA, assessed at 2- and 5-year follow-up time-points, as part of self-reported knee and hip questionnaires.”

“Ipsilateral Knee/Hip involvement and Multivariable-adjusted Outcomes after Primary THA/TKA
- Patients with activity limitation related to ipsilateral knee involvement had 130% higher adjusted odds of moderate-severe index THA pain at 2-years and 80% higher odds at 5-years post-primary THA, both statistically significant (Table 3). Ipsilateral knee involvement increased the odds of moderate-severe functional limitation by 210% at 2-years and 250% at 5-years post-primary THA.
- Patients with activity limitation related to ipsilateral hip involvement significantly increased the odds of moderate-severe index TKA pain by 230% at 2-years and 80% at 5-years after primary TKA (Table 3). Patients with ipsilateral hip involvement had 260% higher odds of moderate-severe functional limitation at 2-years and 120% higher odds at 5-years post-primary TKA.”

6. Covariates of Interest
- Item (7) – the authors say “assessed by same questions as detailed above
preoperatively”. Do the authors mean post operatively here?
Response: The statement as currently stated is corrected, we have modified it a bit to clarify it further. Both pain and function were assessed pre- and post-operatively (2- and 5-years), with similar questions. The postoperative questions are shown under covariates of interest and preoperative questions were similar to the postoperative pain and function questions.
“Pre-operative moderate-severe pain or function: assessed by similar questions as detailed above (under outcomes of interest) preoperatively…..”

7. Statistical Analyses
   I am unable to comment on this.
Response: We have clarified the two paragraphs, as these represent the characteristics of responders and non-responders to the survey to assess characteristics associated with non-response to assess the response bias (as discussed on the limitations section). As in our response to a similar comment above, the three strategies were instituted to increase patient response, and the characteristics presented represent those that did or did not respond to the survey with the combination of the three approaches. Individual response rates are provided in response to a similar comment above.

8. Non-response Bias
   Paragraphs 2 and 3, although they make sense, I find them hard to read and understand easily and perhaps could be reworded to improve on clarity.
   Also as commented earlier it would be interesting within this “non-response” section to know what method of contact produced the best results in terms of having the lowest non-response.
Response: We have clarified the two paragraphs, as these represent the characteristics of responders and non-responders to the survey to assess characteristics associated with non-response to assess the response bias (as discussed on the limitations section).

9. Discussion
   End of paragraph 2 authors say “Whether treatment of ipsilateral knee/hip involvement with physical therapy or other modalities can improve index THA/TKA remains to be seen”. Again it would be important to know what was meant by involvement, how often was this involvement due to a degenerative change that could be simply addressed by the appropriate arthroplasty and how many were due to previous arthroplasty. A previous arthroplasty could be failing and could respond to revision surgery.
Response: We have clarified this as suggested. We thank the reviewer and have added some context to the discussion, as suggested by the reviewer.
“Whether treatment of activity limitation related to ipsilateral knee/hip with physical therapy, surgical (i.e. arthroplasty) or other modalities can improve index THA/TKA outcomes remains to be seen. Several underlying conditions can lead to the activity limitation related to ipsilateral knee/hip involvement, such as: (1) due to multiple joint osteoarthritis or other arthritis, in patients with primary THA and TKA; (2) due to failing primary or revision arthroplasty in the ipsilateral joint in those with primary or revision arthroplasty; and (3) diseases of peri-articular structures, such as bursitis, tendinitis, that
lead to articular and peri-articular symptoms.”

10. In the final paragraph “In summary, we found that ipsilateral knee/hip involvement at the time of surgery was a significant predictor of poor pain and function limitation after primary THA/TKA”. It is not clear in the Methods as to whether or not the questions about ipsilateral knee/hip involvement were asked at all three time intervals. This comment would seem to imply that it was just asked at the time of surgery and not at the two and five year intervals.

Response: We regret the error and have corrected it. The reviewer is absolutely correct that these measures were measured at the follow-up time period, not pre-operatively.

“Several underlying conditions can lead to the activity limitation related to ipsilateral knee/hip involvement, such as: (1) due to multiple joint osteoarthritis or other arthritis, in patients with primary THA and TKA; (2) due to failing primary or revision arthroplasty in the ipsilateral joint in those with primary or revision arthroplasty; and (3) diseases of peri-articular structures, such as bursitis, tendinitis, that lead to articular and peri-articular symptoms. Future studies should assess whether the treatment of ipsilateral joint involvement leads to improvement in outcomes related to index TKA/THA joint. Whether treatment of activity limitation related to ipsilateral knee/hip with physical therapy, surgical (i.e. arthroplasty) or other modalities can improve index THA/TKA outcomes remains to be seen.”

11. Overall Comments
This is a well written paper. Essentially the authors found that ipsilateral knee or hip involvement at the time of surgery was a significant predictor of poor pain and functional limitation after primary THA/TKA. Although perhaps these conclusions are predictable as the authors also say there are no published studies describing the effect of ipsilateral lower extremity joint involvement on patient-reported outcomes after hip or knee arthroplasty. I consider the paper worthy of publication without any major changes.

Response: We thank the reviewer for his kind comments and excellent suggestions. We agree with the reviewer that this paper addresses a key area (ipsilateral joint involvement) of outcomes knee and hip arthroplasty for the first time and provides new findings.
Reviewer's report: Title: Ipsilateral Lower Extremity Joint Involvement Increases the Risk of Poor Pain and Function Outcomes after Hip or Knee Arthroplasty Version: 2
Date: 21 March 2013 
Reviewer: Hassan Ghomrawi

The authors tackle an important topic in total joint replacement. Other joint “pains and limitations” have received little attention in the literature despite being intuitively affecting patient perceptions.

1. Major compulsory revisions
   The authors describe the Mayo Clinic total joint replacement registry rather in general terms without providing specific inclusion/exclusion criteria beyond “Patients were included in this study if they had undergone a primary or revision THA or TKA during 1993-2005 and had responded to both pre- and at least one-post-surgery questionnaire (2- or 5-year follow-up).”
   Based on these criteria, the reviewer is not clear whether ipsilateral involvement was present at baseline when the index surgery was performed or not. If so, this involvement would have also affected the baseline reporting.
   Response: We provide the inclusion and exclusion criteria more clearly, as suggested by the reviewer.
   “Study inclusion criteria were (1) Patients had undergone a primary or revision THA or TKA during 1993-2005 at Mayo Clinic, Rochester, Minnesota; and (2) had responded to both pre-surgery Mayo Hip or Knee questionnaire and at least one post-surgery Mayo Hip or Knee questionnaire (either 2- or 5-year follow-up survey).

2. It is also not clear whether the ipsilateral joint of interest had a total joint replacement or not. In other words, it is not clear whether the pain is resulting from a deteriorating total joint replacement (that was not performed at Mayo) or from a degenerative disease of the joint.
   Response: The reviewer brings up an important point, that unlike in National Health care systems in Scandinavia and the Europe, where all health care of patient can be tracked using national records, no such single system exists in the US; there is no established national US total joint registry that can provide such data. Therefore procedures done outside can be easily missed. This limitation also applies to our Joint registry, which we discuss as follows. In addition, detailed information on pathology on the other joint is not captured, another limitation of the registry, which we discuss now. The reviewer is correct and we agree that the ipsilateral joint involvement could be due to OA or prior arthroplasty in the ipsilateral joint, which we also discuss now.
   “Several underlying conditions can lead to the activity limitation related to ipsilateral knee/hip involvement, such as: (1) due to multiple joint osteoarthritis or other arthritis, in patients with primary THA and TKA; (2) due to failing primary or revision arthroplasty in the ipsilateral joint in those with primary or revision arthroplasty; and (3) diseases of peri-articular structures, such as bursitis, tendinitis, that lead to articular and peri-articular symptoms. Future studies should assess whether the treatment of ipsilateral joint involvement leads to improvement in outcomes related to index TKA/THA.
joint. Whether treatment of activity limitation related to ipsilateral knee/hip with physical therapy, surgical (i.e. arthroplasty) or other modalities can improve index THA/TKA outcomes remains to be seen.

“The joint registry does not provide detailed data on disease pathology in all other joints, and may miss interval arthroplasty in the ipsilateral joint, if done at another institution and not reported by the patient during mailed survey of telephone interview. Therefore, we are unable to comment on the underlying disease/pathophysiology responsible for ipsilateral joint involvement.”

3. Can the authors explain why they have not excluded inflammatory arthritis patients in the analysis? Other joint involvement is very prevalent in these patients, unlike OA patients.
Response: We decided a priori to include all patients in our analyses to have greater generalizability of our findings. Therefore, patients with arthritis other than OA were included. As suggested by the reviewer, we performed sensitivity analyses by excluding patients with rheumatoid arthritis/inflammatory arthritis to check the robustness of results. The results were similar in this sensitivity analyses and have been added to the results and discussion sections. We have added an appendix to show these results (Appendix 1). These findings are not surprising since 90-95% patients in our cohorts had OA.

### Original analyses

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<td>Moderate severe pain (Ref, None)</td>
<td>2.3 (1.5, 3.6)</td>
<td>&lt;0.001</td>
<td>1.8 (1.1, 2.7)</td>
<td>&lt;0.</td>
<td>3.3 (2.3, 4.7)</td>
<td>0.01</td>
<td>1.8 (1.1, 2.7)</td>
<td>0.01</td>
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<tr>
<td>Moderate severe functional limitation (Ref, None)</td>
<td>3.1 (2.3, 4.3)</td>
<td>&lt;0.001</td>
<td>3.6 (2.6, 5.0)</td>
<td>&lt;0.</td>
<td>3.6 (2.6, 4.9)</td>
<td>0.001</td>
<td>2.2 (1.6, 3.2)</td>
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### Sensitivity analyses limited only to OA patients

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<tr>
<td>Moderate severe pain (Ref, None)</td>
<td>2.2 (1.4, 3.1)</td>
<td>0.00</td>
<td>1.9 (1.1, 3.0)</td>
<td>0.0</td>
<td>3.4 (2.4, 4.9)</td>
<td>0.001</td>
<td>1.8 (1.1, 2.8)</td>
<td>0.12</td>
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<tr>
<td>Moderate severe functional limitation (Ref, None)</td>
<td>3.1 (2.2, 4.2)</td>
<td>&lt;0.001</td>
<td>3.7 (2.6, 5.2)</td>
<td>&lt;0.</td>
<td>3.6 (2.6, 4.9)</td>
<td>0.001</td>
<td>2.3 (1.6, 3.2)</td>
<td>0.001</td>
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4. Also, the authors acknowledge the effect of contralateral joint involvement on reporting for the index joint. It is unclear, given the large volume of patients in the Mayo clinic registry, why the authors have not excluded patients with contralateral joint pain or adjusted for this variable in the analysis.

Response: We performed sensitivity analyses by excluding patients with contralateral joint involvement, as suggested by the reviewer. The results and interpretation did not change much. For example, for primary TKA, the odds ratios for association of ipsilateral hip involvement with moderate-severe limitation were 3.3 (2.1, 5.1; p<0.001) at 2-years and 2.3 (1.4, 3.7; p<0.001), similar to the odds ratios of 3.6 and 2.2 (as in the table for the main analyses; please see that able in the response to the comment right above). “Sensitivity analyses that excluded patients with contralateral joint involvement showed minimal change in odds ratio and no change in the level of significance.”

5. The multivariable regression adjusts for a bunch of variables, most of which are traditional in these studies. The reviewer does not understand why distance from medical center is an important variable to adjust for in the model. If the authors believe it is important, they should provide an explanation.

Response: We provide the rationale now, as follows. “Distance from the medical center- <100, 100-500 and >500 miles/overseas: distance from the medical center was included, since Mayo Clinic provides TKA/THA to local residents, but also a serves as a referral center for patients traveling from far, who may have different disease severity and expectations, and both can impact pain and function outcomes;

6. The authors correctly acknowledge the presence of response bias in their study and are commanded for this, especially given that the response rates go as low as 48%. They report important differences between respondents and non-respondents in their results section. The authors are strongly advised to take advantage of statistical methods to adjust for bias to determine if the results would change.

Response: We agree with the reviewer that the 5-year response rates were low, ranging 48-57%. We acknowledge this limitation in the limitations section. The 2-year response rates were 57-65%, well in the range of average of 60% in large epidemiological surveys of this size. We provide our interpretation of non-response bias in the discussion section. We considered the multiple imputation method to adjust for non-response bias, but decided not to use it, because of our missing data are not missing at random and there is a likelihood of introducing more bias as compared to the completed case analyses. According to a recent review of use and misuse of multiple imputation methods, Sterne et al. commented “When data are missing not at random, bias in analyses based on multiple imputation may be as big as or bigger than the bias in analyses of complete cases.”

“Non-responders were more likely to be younger, obese, higher comorbidity, higher ASA class and live at a greater distance from the Mayo Clinic, characteristics associated with poorer pain and functional outcomes after THA/TKA. However, it is unlikely that the association of ipsilateral joint involvement with index THA/TKA pain and function outcomes differed by these characteristics, in absence of any such published data. Therefore, the direction of impact of non-response bias is unclear.”
Reviewer’s report: **Title:** Ipsilateral Lower Extremity Joint Involvement Increases the Risk of Poor Pain and Function Outcomes after Hip or Knee Arthroplasty **Version:** 2
**Date:** 27 March 2013 **Reviewer:** Michael A. Mont **Reviewer’s report:**

1. Manuscript acceptable without revision. **Quality of written English:** Acceptable. **Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Response:** We thank the reviewer for his kind comments. We agree that this paper provides new knowledge of interest to the readers.

References: